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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/053,975	01/18/2002	Limin Li	FUNC-0020-UT1	5176

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	
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05/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/053,975	LI ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/09/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-16,22-25,31,32 and 37-50* is/are pending in the application.

4a) Of the above claim(s) *7-16,22-25,31,32,37-42,44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-6, 43 and 46-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 4/09/2009 in response to the previous Non-Final Office Action (1/09/2009) is acknowledged and has been entered.

Claims 1, 4-16, 22-25, 31-32 and 37-50 are pending.

Claims 7-16, 22-25, 31-32, 37-42 and 44-45 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1, 4-6, 43 and 46-50 are currently under consideration.

Rejections maintained, but amended for clarification:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 43, 46 and 49-50 remain rejected under 35 U.S.C. 102(b) as being anticipated by Li et al. (IDS, US 5,891,668, 1999).

Li. et al. teach antibodies which have been raised to normal or mutated forms of TSG101 (column 8, line 59-63). Specifically, the patent teaches antibodies that specifically recognize an epitope within the coiled domain, leucine zipper and proline rich domains of TSG101 (column 8, lines 64 to column 9, line 4). In particular, the patent teaches (column 3, line 45) that the proline rich domain encompasses amino acids 130-205 of human TSG101, e.g., amino acids 140-215 of the claimed SEQ ID NO: 1. Moreover, the patent teaches that the antibodies include, but are not limited to, polyclonal antibodies and monoclonal antibodies (column 9, lines 5-21). With regards to TSG101, Li et al. provide both the mouse TSG101 and the human homolog (column 3, lines 26-38, see below, human homolog). The patent further teaches that the antibodies find particular use in diagnostic assays for carcinomas, wherein staging, detection and typing of tumors may utilize a quantitative immunoassay for the present of absence of TSG101 (column 9, lines 22-29). Thus, while the prior art does not explicitly teach that the antibody is in a composition further comprising

pharmaceutically acceptable excipients, it would necessarily flow from the teachings of the prior art that the antibody is in a composition comprising an excipients such as a buffer. Note: the recitation of "for treatment of diseases involving TSG101-mediated ubiquitination" is an intended use of the claimed composition and has not been give any patentable weight. Applicants are reminded that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

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Patent No. 5891668
APPLICANT:  LI, Limin
APPLICANT:  COHEN, Stanley N
US-08-670-274B-4

  Query Match             97.8%;  Score 2002;  DB 2;  Length 380;
  Best Local Similarity   100.0%;  Pred. No. 3e-155;
  Matches  380;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          11 MVSKYKYRDLTVRETVNVITLYKDLKPVLDSYVFNDGSSRELMNLTGTIPVPYRGNTYNI 70
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db           1 MVSKYKYRDLTVRETVNVITLYKDLKPVLDSYVFNDGSSRELMNLTGTIPVPYRGNTYNI 60

Qy          71 PICLWLLDTYPYNPPICFVKPTSSMTIKTGKHVDANGKIYLPYLHEWKHPQSDLLGLIQV 130
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          61 PICLWLLDTYPYNPPICFVKPTSSMTIKTGKHVDANGKIYLPYLHEWKHPQSDLLGLIQV 120

Qy         131 MIVVFGDEPPVFSRPISASYPPYQATGPPNTSYMPGMPGGISPYPSGYPPNPSGYPGCPY 190
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         121 MIVVFGDEPPVFSRPISASYPPYQATGPPNTSYMPGMPGGISPYPSGYPPNPSGYPGCPY 180

Qy         191 PPGGPYPATTSSQYPSQPPVTTVGPSRDGTISEDTIRASLISAVSDKLRWRMKEEMDRAQ 250
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         181 PPGGPYPATTSSQYPSQPPVTTVGPSRDGTISEDTIRASLISAVSDKLRWRMKEEMDRAQ 240

Qy         251 AELNALKRTEEDLKKGHQKLEEMVTRLDQEVAEVDKNIELLKKKDEELSSALEKMENQSE 310
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         241 AELNALKRTEEDLKKGHQKLEEMVTRLDQEVAEVDKNIELLKKKDEELSSALEKMENQSE 300

Qy         311 NNDIDEVIIPTAPLYKQILNLYAEENAIEDTIFYLGEALRRGVIDLDVFLKHVRLLSRKQ 370
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         301 NNDIDEVIIPTAPLYKQILNLYAEENAIEDTIFYLGEALRRGVIDLDVFLKHVRLLSRKQ 360

Qy         371 FQLRALMQKARKTAGLSDLY 390
               ||||||||||||||||||||
Db         361 FQLRALMQKARKTAGLSDLY 380
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In response to the rejection, Applicants contend that claims 1, 6 and 43 now require that the antibody bind to the ubiquitination region to an epitope in the region so indicated, but also modulate the interaction between TSG101 and MDM2, an important interaction in the cell cycle machinery. Thus, Applicants contend that it goes without saying that neither Li et al., nor any other

reference of record, suggest that an antibody could be prepared directed against ANY epitope which modulates this important interaction, and thereby modulates ubiquitination. Moreover, Applicants contend that the assay results set forth in the specification make it clear that not ALL antibodies that bind TSG101 in this region modulate that interaction, or otherwise control ubiquitination. Indeed, Applicants submit that the reference newly cited by the Office, Ferrer et al., makes the point that antibodies raised against TSG101 that bind in the region 54, will not recognize TSG101, and not modulate this interaction (see paragraph bridging the columns of pages 2257, as well as the discussion on page 2258, which indicates that TSG101 alone may block ubiquitination). Accordingly, Applicants assert that it is clear that an antibody which modulates the interaction between TSG101 and MDM2 provides a key function, one not inherent in the generic disclosure of Li et al., which indicates in relevant part only that the proline rich domain of TSG101 may be a good target for antibodies as epitopes. Thus, Applicants contend that since not all antibodies directed to this region will not modulate the interaction between TSG101 and MDM2, and therefore, ubiquitination, these claims are not met. With respect to claims 43 and 50 (rejected in the previous office action), Applicants submit that the limitation of an antibody together with a pharmaceutically acceptable excipients are not met. In particular, Applicants assert that the claims require the excipient or carrier because they are intended as pharmaceutical compositions for the treatment of TSG101 dependent diseases-cancers, virus, ect. As such, Applicants assert that they must be suitable for administration to a mammal, including humans. However, Applicants contend that Li et al. ascribes to the antibodies generally referred to, but nowhere exemplified, only diagnostic value, to be done in vitro.

These arguments have been carefully considered, but have not been found persuasive.

First, the Examiner acknowledges and appreciates Applicants for incorporating the limitation of "and so binding, said antibody modulates interaction between said TSG101 protein or functional fragment thereof and MDM2 protein". However, the Examiner recognizes that this limitation has not been given any patentable weight since the limitation only appears to describe the end result of antibody binding and Applicants have not provided any evidence that not all antibodies that bind to an epitope within the ubiquitination-regulating domain of TSG101 protein found in amino acid residues 1-250 of SEQ IDNO: 1 will not modulate the interaction between said human TSG101 protein and an MDM2 protein. In particular, Applicants contend that support for this

notion can be found in the assays found in the specification. Yet, a careful review of the specification, as originally filed, does not appear to support Applicants assertions. In other words, Applicants have not provided any evidence that an antibody which specifically recognizes the proline rich domain encompasses amino acids 130-205 of human TSG101 as taught by Li et al., e.g., amino acids 140-215 of the claimed SEQ ID NO: 1, will not modulate the interaction of TSG101 and MDM2. Applicants are reminded that the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Similarly, with regards to Applicants assertions that the teachings of Ferrer et al. support Applicants assertions that not all antibodies that bind to an epitope within the ubiquitination-regulating domain of TSG101 protein found in amino acid residues 1-250 of SEQ IDNO: 1 will not modulate the interaction between said human TSG101 protein and an MDM2 protein, the Examiner acknowledges and has carefully reviewed the sections pointed out by Applicants. However, it is unclear how these sections are relevant to the present case. For example, the paragraph bridging the columns of pages 2257 of Ferrer et al. teach that the new protein isoform, e.g., TSG101B, cannot be detected by the available antibody because it was generated against the antibodies raised against amino acids residues 136-374 of TSG101A, e.g., human TSG101 which must recognize an epitope comprised within the deleted amino acid residues, 54 and 311, in the TSG101B isoform. In other words, the epitope which is recognizes by the antibody has been deleted in TSG101B. In contrast, the amino acid residues which comprise the proline rich domain of Li et al. TSG101 are conserved within the claimed TSG101 of SEQ ID NO: 1. As such, it would flow that an antibody which specifically recognizes an epitope in the proline rich domain of Li et al. TSG101 would recognize an epitope within the proline rich domain of the claimed TSG101. With regards to Applicants assertions that Li et al. does not teach a pharmaceutical composition for treatment of diseases involving TSG101-mediated ubiquitination comprising an antibody and a pharmaceutical acceptable excipient, the Examiner acknowledges and does not dispute Applicants assertions that Li et al. does not disclose a pharmaceutical composition as claimed, e.g., for the

treatment of a disease. However, the Examiner recognizes that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In the present case, Li et al., as noted by Applicants, disclose antibodies for diagnosis, typing and staging of human tumors, e.g., breast carcinomas. As such, it would necessarily flow from the teachings of the prior art that the antibody is in a composition comprising an excipients such as a buffer.

New Rejections upon further consideration:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 43 and 46-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims recite an isolated monoclonal antibody that binds specifically to a polypeptide comprising a ubiquitination-regulating domain or a functional fragment thereof, wherein said antibody binds specifically to an epitope in the ubiquitination-regulating domain of TSG101 protein found in amino acids 1-250, 50-140 or 1-140 of SEQ ID NO: 1. Thus, in addition to a protein comprising a ubiquitination-regulating domain found in amino acids 1-250, 50-140 or 1-140 of SEQ ID NO: 1, the claims broadly encompass functional fragments of a ubiquitination domain. Therefore, the claims encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant,

identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164). The specification teaches that as used herein, a functional fragment of an ubiquitination conjugase-like Ubc domain refers to any fragment of the Ubc domain that regulates ubiquitination. Fragments having such activity are readily determined by, e.g., methods as described in the application. In one embodiment, the ubiquitination-regulating domain comprises amino acid residues 1-140 of a human TSG101 protein, e.g., amino acid residues 1-140 of SEQ ID NO: 1. In another embodiment, the ubiquitination-regulating domain comprises amino acid residues 50-140 of a human TSG101, e.g., amino acid residues 50- 140 of SEQ ID NO: 1. In still another embodiment, the ubiquitination-regulating domain comprises amino acid residues 140-250 of a human TSG101, e.g., amino acid residues 140-250 of SEQ ID NO: 1. In still other embodiments, the ubiquitination-regulating domain may comprises, e.g., amino acid residues 10-140, 20-140, 30-140, 40-140, 1-160, 1-180, 1-200, 1-220, 50-250 or 1-250 of a human TSG101, e.g., amino acid residues 10- 140, 20-140, 30-140, 40-140, 1-160, 1-180, 1-200, 1-220, 50-250 or 1-250 of SEQ ID NO:1 (page 12, 1st full paragraph). Accordingly, there is insufficient written description encompassing a "functional fragment" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "functional fragment" are not set forth in the specification as-filed, commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

In the absence of structural characteristics that are shared by members of the genus of a "functional fragments"; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Claims 43 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands

states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are a pharmaceutical composition for the treatment of diseases involving TSG101 mediated ubiquitination comprising: an isolated antibody that specifically binds to a polypeptide comprising an ubiquitination-regulating domain, or functional fragment thereof. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a pharmaceutical composition for the treatment of diseases involving TSG101 mediated ubiquitination comprising: an isolated antibody that specifically binds to a polypeptide comprising an ubiquitination-regulating domain, or functional fragment thereof. Thus, the claims imply that the pharmaceutical composition can be used for the treatment of diseases such as cancers, viruses, ect. (see Applicants response).

Guidance in the specification and Working Examples

The specification teaches that the present invention provides methods of treating a subject of a proliferative disorder comprising administering a therapeutically effective amount of an agent that is capable of modulating the interaction between TSG101 and MDM2 (page 24, 2nd full paragraph). With regards to the agents, the specification teaches that the agents include, but are not limited to, antibodies (page 16, 2nd full paragraph). Thus, while the specification contemplate the use of the antibodies for the treatment of a disease state associated with TSG101, the specification appears to be silent on any in vitro or in vivo examples demonstrating treatment of a disease with a pharmaceutical composition comprising an isolated antibody that specifically binds to a polypeptide comprising an ubiquitination-regulating domain, or functional fragment thereof. While it is understood that the absence of working examples should never be the sole reason for rejecting a

claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that TSG101 is involved in tumorgenesis. For example, Li et al. (US 5,891,668, 1999, of record) teach that sporadic deletions in TSG101 are associated with the occurrence of human cancers, for example breast carcinomas (column 2, lines 28-29). As such, Li et al. teach that TSG101 is a target for both therapy and diagnosis (column 9, lines 1-4 and column 11, lines 6-7). Thus, while the patent contemplates the use of TSG101 as a target for therapy, the patent appears to be silent on any in vivo examples.

With regards to the unpredictability in the art, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell

interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. In addition, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Those of skill in the art also recognize the unpredictability of treating tumors with antibodies. For example, Jain (Scientific American July 1994), discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, in the late 80's, Dillman (Annals of Internal Medicine, Volume 111, pages 592-603, 1989) summarized (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite

advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). More recently, Weiner (Seminars Oncology, Vol. 26, No.4, 1999, pages 41-50) provided an overview of monoclonal antibody of therapy including some promising activity, however major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets, insufficient target specificity, and induction of HAMA (page 43). The above obstacles are further compounded by the fact that, in this case, the target (ST receptor) is present on both normal and cancerous cells. Hence, in the words of Weiner there is a total lack of target specificity. For instance, the claims are drawn to "treating" an individual suspected of suffering from colorectal cancer. This treatment necessarily includes administration of a ligand to the ST receptor along with a cytotoxin. However, the specification teaches (page 6, lines 1+) that expression of the ST receptor is *not limited* to colorectal cancer cells. For example, the specification teaches "In normal individuals, ST receptors are found exclusively in cells of the intestine, in particular in cells in the duodenum, small intestine (jejunum and ileum), the large intestine, colon (cecum, ascending colon, transverse colon, descending colon and sigmoid colon) and rectum."

Moreover, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high

skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-5 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (IDS, US 5,891,668, 1999) as applied to claims 1, 6, 43, 46 and 49-50 above, and further in view of Ferrer et al. (Oncogene 1999; 18: 2253-2259, IDS).

Li. et al. teach antibodies which have been raised to normal or mutated forms of TSG101 (column 8, line 59-63). Specifically, the patent teaches antibodies that specifically recognize an epitope within the coiled domain, leucine zipper and proline rich domains of TSG101 (column 8, lines 64 to column 9, line 4). In particular, the patent teaches (column 3, line 45) that the proline rich domain encompasses amino acids 130-205 of human TSG101, e.g., amino acids 140-215 of the claimed SEQ ID NO: 1. Moreover, the patent teaches that the antibodies include, but are not limited to, polyclonal antibodies and monoclonal antibodies (column 9, lines 5-21). With regards to TSG101, Li et al. provide both the mouse TSG101 and the human homolog (column 3, lines 26-38, see below, human homolog). The patent further teaches that the antibodies find particular use in diagnostic assays for carcinomas, wherein staging, detection and typing of tumors may utilize a quantitative immunoassay for the present of absence of TSG101 (column 9, lines 22-29).

Li et al. do not specifically teach monoclonal antibodies raised against amino acids 1-130 of human TSG101, e.g., amino acids 10-140 of SEQ ID NO: 1.

Ferrer et al. teach that normal human TSG101 contains the ubiquitin regulatory homology domains near the N-terminus, e.g., amino acids 1-134 of human TSG101, and a canonical leucine zipper with seven leucin residues more proximal to the carboxy terminus, wherein the regions

URH1 (ubiquitin regulatory-protein homology 1) and URH2a are the most conserved and specific for the E2 ubiquitin inhibitors, while the complete region (URH2 and 3) are homologous with the E2 family of proteins as a group and absent in a mutated form of TSG101 found expressed in a variety of cancers (page 2255, 1st column, 2nd full paragraph and Figure 4).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the reference so as generate monoclonal antibodies as taught by Li et al. to amino acids 1-134 of human TSG101 in view of the teachings of Ferrer et al. One would have been motivated to do so because as taught by Ferrer et al. those of the skill in the art recognize that the regions URH1 (ubiquitin regulatory-protein homology 1) and URH2a are the most conserved and specific for the E2 ubiquitin inhibitors, while the complete region (URH2 and 3) are homologous with the E2 family of proteins as a group. Moreover, the Board of Patent Appeals and interferences has taken the position that once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious. See Ex parte Erlich, 3 USPQ 2d 1011 (PTO Bd. Pat. APP. & Int. 1987), Ex parte Sugimoto, 14 USPQ 2d 1312 (PTO Bd. Pat. APp. & Int. 1990).

In response to this rejection, Applicants assert that Li et al. discusses three specific domains for epitopes, and in effect teaches specifically away from the claimed invention. For instance, Applicants assert that Li et al. does not teach that antibodies to any domain of TSG101 would be of value, including e.g., 1-140, but some would be better. Applicants further contend that the Examiner notes that Ferrer et al. teaches that there is an N-terminus domain in a mutant TSG101 that contains a ubiquitin regulatory region similar to that of normal TSG101, and a leucine zipper different from that of wildtype TSG101. Thus, Applicants assert so what. In particular, Applicants contend that Ferrer et al. does not teach that either of these regions make a good target for an antibody. Moreover, Applicants assert that nowhere does this assemblage of art teach the preparation of antibodies that bind in these regions. Additionally, Applicants question why would one of skill in the art go against the teachings of Li et al, and assert that the action does not explain this. Thus, Applicants contend that the present claims are directed to a very specific part of that protein, a part not only not identified as of interest or antigenic or valuable as an epitope, but in fact taught away from as an epitope.

These arguments have been carefully considered, but are not found persuasive.

In the present case, the majority of Applicants arguments appear to argue the references individually without addressing the combination as they are written. Applicants are reminded that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Moreover, with respect to the motivation, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation

to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the present case, Li et al. teach antibodies which have been raised to normal or mutated forms of TSG101, wherein the antibodies find particular use in diagnostic assays for carcinomas. Li et al. does not teach monoclonal antibodies raised against amino acids 1-130 of human TSG101, e.g., amino acids 10-140 of SEQ ID NO: 1. However, Ferrer et al. teach that normal human TSG101 contains the ubiquitin regulatory homology domains near the N-terminus, e.g., amino acids 1-134 of human TSG101, wherein the regions URH1 (ubiquitin regulatory-protein homology 1) and URH2a are the most conserved and specific for the E2 ubiquitin inhibitors. Thus, one of skill in the art would have a reasonable expectation of success that by raising monoclonal antibodies against amino acids 1-130 of human TSG101, e.g., amino acids 10-140 of SEQ ID NO: 1, one would achieve an antibody for diagnostic purposes.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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